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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/786,988	01/23/1997	DANIEL P. LITTLE	U/18485-0012	5922

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EXAMINER

BEX, PATRICIA K

ART UNIT

PAPER NUMBER

1743

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

MFO

<b>Office Action Summary</b>	Application No.	Applicant(s)
	08/786,988	LITTLE ET AL.
	Examiner	Art Unit
	P. Kathryn Bex	1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 16 October 2001.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-6,9-34,40-51 and 54-94 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-6,9-34,40-51 and 54-94 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 11 January 2002 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.

2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 36, 37. 6) Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Continued Prosecution Application***

1. The request filed on October 16, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/786,988 is acceptable and a CPA has been established. An action on the CPA follows.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
3. Claims 1-6, 9-34, 40-51 and 54-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for capillaries capable of dispensing within the range of 0.2-2 nL, does not reasonably provide enablement for the vesicle to dispense in the "sub to low" range. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. The specification does not support the broad limitation of "sub to low" range, but rather sites a specific range i.e. 0.2-2 nL. Therefore, the specification does not enable one of ordinary skill to make/use the invention commensurate in the scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6, 9-34, 40-51 and 54-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, now recites the vesicle to eject from the chamber a "sub to low" nanoliter volume. The terms "sub" and "low" are relative terms which render the claim indefinite. The terms "sub" and "low" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to what Applicant considers a "sub" or "low" amount of nanoliter volume.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-6, 9-34, 40-51, 54-69 and 87-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tisone (USP 5,743,960) in view of Jespersen *et al* (Attomole detection of Proteins by Matrix-assisted Laser Desorption/Ionization Mass Spectrometry with the Use of Picoliter Vials) or Li *et al* (Analysis of Single Mammalian Cell Lysates by Mass Spectrometry).

Tisone discloses a method and an apparatus for dispensing a material on a substrate substantially as claimed. The method comprises the steps of providing a vesicle 12 having an interior chamber containing a fluid, disposing the vesicle 12 adjacent a first location on the surface of a substrate 30, controlling the vesicle to eject from the chamber a sub to low nanoLiter volume, i.e. less than 0.54 nanoliter, (column 8, lines 35-46) of the fluid to dispense the fluid at the first location of the surface of the substrate. Next moving the vesicle to a set of positions so that fluid is dispensed from the vesicle at each location of the set for forming an array of fluid material (Figs. 1, 6-7). Note: that Tisone *et al* teach in one of the embodiments that the method can be used to dispense sample fluids onto a diagnostic test strip for testing (column 11, lines 14-25). Tisone *et al* do not specifically recite the step of performing mass spectrometry analysis for the material. However, such an analysis step on a substrate using a mass spectrometer is considered conventional in the art, see Jespersen *et al* or Li *et al*.

Jespersen *et al* teaches an apparatus and method for the detection of biomolecules by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Jespersen *et al* recognizes the significant improvement in the absolute detection limits attainable by the reduction of the sample volume from a few microliters down to 250 picoliters. Jespersen *et al* teach use of an array picoliter vials etched onto a silicon wafer. This silicon wafer is glued onto a MALDI stainless-steel target for detection by the mass spectrometer. The picoliter vials were filled manually under an optical microscope using laboratory-made glass micropipettes, resulting in pipettes with an outer tip diameter smaller than 100 micrometers.

Similarly, Li *et al* teach a MALDI mass spectrometry in combination with a capillary loaded with sample to deposit sample on a probe surface. Using capillaries with internal

diameters from 10-200 micrometers, the volume delivered can be varied over a wide range (i.e. 20 picoliter to 100 nanoliters). The capillaries dispensing the sample spots onto the matrix layer for analysis by a high-resolution TOF-MS.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method and apparatus of applying nanoliter volumes as taught by Tisone *et al* with detection system, as taught by Jespersen *et al* or Li *et al*, in order to provide a significant reduction of both the sample volume needed and three orders of magnitude improvement in detection limits (see third full paragraph of Jespersen *et al*).

8. Claims 70-86 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ershow *et al.* (USP 5,756,050) in view of Jespersen *et al* (Attomole detection of Proteins by Matrix-assisted Laser Desorption/Ionization Mass Spectrometry with the Use of Picoliter Vials) or Li *et al* (Analysis of Single Mammalian Cell Lysates by Mass Spectrometry).

Ershow *et al* disclose an apparatus and method for dispensing sub to low nanoLiter volumes, i.e. 0.3 nanoliter, (column 3, lines 1-4) of a material on the surface of a substrate 16 substantially as claimed. The method comprises the steps of providing a pin assembly 1 having a plurality of elongated vesicles 2 arranged as an array for dispensing a liquid therefrom (Figs. 1-2), wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoLiter volume for fluid; loading a volume of fluid from a fluid source 14 onto the end of the vesicles; disposing the pin assembly to align the vesicles at a first set of locations adjacent to the surface of the substrate 16; and contacting the loading fluid to the surface of the substrate is formed (Figs. 3-4). Ershow *et al.* fail to specifically recite a diagnostic tool comprising a mass

spectrometer. However, the use of such a spectrometer for identifying polymers is considered conventional in the art, see Jespersen *et al* or Li *et al*.

Jespersen *et al* teaches an apparatus and method for the detection of biomolecules by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Jespersen *et al* recognizes the significant improvement in the absolute detection limits attainable by the reduction of the sample volume from a few microliters down to 250 picoliters. Jespersen *et al* teach use of an array picoliter vials etched onto a silicon wafer. This silicon wafer is glued onto a MALDI stainless-steel target for detection by the mass spectrometer. The picoliter vials were filled manually under an optical microscope using laboratory-made glass micropipettes, resulting in pipettes with an outer tip diameter smaller than 100 micrometers.

Similarly, Li *et al* teach a MALDI mass spectrometry in combination with a capillary loaded with sample to deposit sample on a probe surface. Using capillaries with internal diameters from 10-200 micrometer, the volume delivered can be varied over a wide range (i.e. 20 picoliter to 100 nanoliters). The capillaries dispensing the sample spots onto the matrix layer for analysis by a high-resolution TOF-MS.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method and apparatus of applying nanoliter volumes as taught by Ershow *et al* with detection system, as taught by Jespersen *et al* or Li *et al*, in order to provide a significant reduction of both the sample volume needed and three orders of magnitude improvement in detection limits (see third full paragraph of Jespersen *et al*).

***Response to Arguments***

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9. Applicant's arguments with respect to claims 1-6, 9-34, 40-51 and 54-94 have been considered but are moot in view of the new ground(s) of rejection. See above Office Action.

***Conclusion***

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Kathryn Bex whose telephone number is (703) 306-5697. The examiner can normally be reached on Mondays-Thursdays, alternate Fridays from 6:00 am to 3:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 308-4037.

The fax number for the organization where this application or proceeding is assigned is (703) 872-9310 for official papers prior to mailing of a Final Office Action. For after-Final Office Actions use (703) 872-9311. For unofficial or draft papers use fax number (703) 305-7719. Please label all faxes as official or unofficial. The above fax numbers will allow the paper to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0661.

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